REMARKS

Claims 58-73 and 84-113 are pending. Claims 58, 66, 72, 73, 84-87, 101, 104, 107 and 108 have been amended. Claims 74-83 have been cancelled. New claims 112 and 113 have been added. Support for the amendments to claims 72 and 73 can be found, for example, at page 32, lines 27-37 and page 33, lines 1-2 and 8-12 of the application. No new matter has been added.

The specification has been amended, thereby obviating the Examiner's objections to the specification. In addition, claims 73, 75, 77, 81 and 83 have been cancelled, thereby obviating the Examiner's objections to these claims.

Rejection of Claims 73 and 79 Under 35 U.S.C.§112, second paragraph

Claims 73 and 79 are rejected under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention."

Claim 79 has been cancelled and claim 73 has been amended, thereby obviating this rejection.

Rejection of Claims 58-111 Under 35 U.S.C. §112, first paragraph

Claims 58-111 are rejected under 35 U.S.C. §112, first paragraph "as failing to comply with the enablement requirement."

In particular, the Examiner states that "the claims are broadly drawn to a method of 'preventing' or 'delaying development' of any and all non-prostate cancers including renal, urothelial, colon, rectal, lung and breast cancers and or metastatic adenocarcinoma to the liver." The claims have been amended to remove the "preventing" and "delaying" language, thereby obviating this rejection.

The Examiner further asserts, "with regards to treatment of subjects with cancer comprising the presently claimed antibodies, the specification does not provide sufficient guidance and or objective evidence that such methods would predictably and effectively treat a subject as claimed."

Applicant respectfully traverses this portion of the rejection.

The Examiner makes several general statements regarding the unpredictability of antibody therapy that are not supported by the cited art and which do not take into consideration Applicant's invention. The arguments seem to be based largely, if not entirely, on a partial and extraordinarily selective reading of Jain et al., a 10 year old report for the non-specialist from a non-specialist journal (Scientific American). The Examiner, relying heavily on certain sections of Jain et al., argues that there are several barriers to delivering drugs to solid tumors, these include "1) non-uniform blood delivery to all areas of the tumor in which some areas receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all ... (3) high liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, to tumors ... (4) convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature." The Examiner concludes that the methods of the invention are not enabled.

Applicant points to several considerations, any one of which show that the rejection is unfounded. These, in no particular order, are as follows:

First, as alluded to above, the Examiner's arguments seem to be based largely, if not entirely, on a partial and selective reading of Jain et al. While there are passages in Jain et al. which point to characteristics of cancer cells which act as "barriers" to treatment, other sections in Jain et al. provide ways of defeating the barriers, and argue that antibodies which bind

endothelial cells (Applicant notes that PSMA is found on the vascular endothelium) are not subject to those barriers. See Jain et al., at page 65, which discusses approaches which would not be defeated by the "barriers" discussed elsewhere in the article:

> Alternatively, if a tumor's vasculature system could be destroyed completely, no drug would have to extravasate or cope with the interstitium. The persistent, total lack of nourishment would be expected to starve and eventually kill tumor cells. A variety of drugs—among them tumor necrosis factor and monoclonal **antibodies that recognize endothelial cells** or the subendothelial matrix—have the potential to shut down the blood supply completely. (emphasis added)

By its own terms, purely by its own internal logic, Jain et al. says that the barriers it proposed do not apply to antibodies which bind endothelial cells. Applicant is not taking the position that the entire vascular system of a tumor (or any part thereof) needs to be destroyed to treat a cancer, that the antibodies of the invention do that, or that any mechanism discussed in Jain et al., e.g., a characteristic said by Jain et al. to overcome such a barrier, applies to the antibodies of the invention. Applicant is not asserting any particular model of action for the antibodies of the invention (other than the fact that they are PSMA-specific). What Applicant argues is that, when read as a whole, and not in an extremely selective way, the reference, by its own terms, does not apply to the antibodies of the invention. Jain et al. may be right or wrong with regard to any of the mechanisms it proposes, but when read as a whole, it does not question the enablement of the antibodies of the invention. Jain et al. first identifies barriers to treatment and then secondly identifies a number of mechanisms which would defeat those barriers, including the use of antibodies which bind to markers on endothelial cells. The Examiner relies heavily on the first and ignores the second. This is impermissible. A reference must be taken for what it teaches as a whole. When considered as a whole, without ignoring critical aspects of the article, one would simply never conclude that Jain et al. suggests the antibodies of the invention would be subject to the barriers discussed in the article.

Second, a review of Jain et al. shows that it did not say that even if present, the barriers proposed therein would be an absolute barrier to the use of blood borne anti-cancer agents. If that were the case then no blood borne anti-cancer agent (other than perhaps members of the small group, e.g., TNF and certain types of antibodies, referred to in Jain et al.) would work, and that is of course simply not true. Despite the misgivings of Jain et al. numerous blood borne anti-cancer agents do work. If we admit, that despite the misgivings of Jain et al., some do work, then, for the Examiner's arguments to have force, there must be something special about the antibodies of the invention that differentiates them and suggests that they could not be used without undue experimentation. The Examiner provides absolutely no reasons why the "barriers" discussed in Jain et al., even if present, would pose a significant or particular problem for anti-PSMA antibodies, as opposed to other anti-cancer agents. The Examiner simply interprets the term "barrier" as being an absolute barrier and that it applies absolutely to the antibodies of the invention, with no support in the art for either the absolute barrier interpretation or its special application to the antibodies of the invention. Indeed if anything, Jain et al., by its own terms, suggests that antibodies, which like anti-PSMA antibodies, bind to targets found on endothelial cells, would work. See the discussion of the passage at page 65 of Jain et al., above, which is incorporated by reference here.

Third, the Applicant has provided a wealth of evidence that the protein (PSMA) bound by anti-PSMA antibodies of the invention, is present on the vascular endothelium of a broad range of cancers. For example, in Example 13 of the present application, Applicant demonstrates that antibodies against the extracellular domain of PSMA bind the neovasculature of renal carcinomas, urothelial carcinomas, colon carcinomas, rectal carcinomas, lung carcinomas, breast cancer, and metastatic adenocarcinoma to the liver. Other malignancies that have neovasculature that expresses PSMA include ovarian, neoendocrine, glioblastomas, melanomas, pancreatic, soft tissue sarcoma and kidney cancers, see the Declaration under 37 CFR 1.132 of Dr. Jeffrey Ross (hereafter referred to as "the Declaration"). Other than the generalizations of the Jain et al.

article, the Examiner has cited no evidence that these would not be available to anti-PSMA antibodies *in vivo*.

Fourth, it has been shown, *in vivo*, in humans, that antibodies against the extracellular domain of PSMA target the vasculature of tumors. Clinical trials using the antibodies of the invention to treat various non-prostate cancers have begun and have demonstrated that the antibodies of the claims achieve effective targeting *in vivo* in human subjects. This has been shown in diverse types of tumors, as is discussed in the Declaration. See, e.g., paragraph 5 of the Declaration, which provides, in pertinent part:

> Human clinical trials, using methods of the invention, have begun. ... Exhibit A shows a CT scan and an indium scan of a patient having renal cancer and receiving ^{111}In labeled J591. As can be seen in Exhibit D, both CT and indium scans demonstrate targeting of J591 to a lung metastases in the subject. Exhibit B demonstrates *in vivo* targeting of ^{111}In labeled J591 to the neovasculture of melanoma in a human subject. Exhibit C demonstrates *in vivo* targeting of ^{111}In labeled J591 to the neovasculture of a colon cancer in a human subject. In my opinion, the data discussed in this Declaration show that the specification provides sufficient guidance to allow one of ordinary skill in the art to practice the claimed invention without undue experimentation.

Fifth, as is shown in Nanus et al., *Clinical use of monoclonal antibody HuJ591 therapy: targeting prostate specific membrane antigen*, Journal of Urology, 2003, 170: S84-S89, et al,. a copy of which is enclosed as Exhibit A, anti-PSMA antibodies of the invention are effective in treating prostate cancer. See, e.g., the first full paragraph, right column, page S87, which provides that anti-tumor effects were seen, *even in phase 1 trials*:

> The primary objectives of these independent trials were to define the maximum tolerated dose, dosimetry, pharmacokinetics and immunogenicity of the ^{90}Y and ^{177}Lu-mAb conjugates. Antitumor responses were assessed as a secondary end point. Dose levels

were escalated in cohorts of 3 to 7 patients with a 6 to 8-week observation period between dose levels. All patients underwent nuclear imaging with either ^{111}In-HuJ591 (patients receiving ^{90}Y, a pure B emitter that does not image on radionuclide scans) or ^{177}Lu-HuJ591 (γ-emitting properties), and the imaging results were compared to standard imaging studies. Preliminary analysis indicated that bone and soft tissue metastases seen on conventional bone scans and CT were accurately targeted by HuJ591 in virtually every patient. No patient has had HAHA in either study. The dose limiting toxicity of myelosuppression in the 90Y-HuJ591 study occurred at a dose of 20mCi/m2 and the ^{177}Lu-HuJ591 is ongoing, with the dose limiting toxicity not yet reached. **Dose related antitumor effects have been noted including PSA and measurable disease responses**. (emphasis added)

Reduction in PSA levels have also been seen with the administration of naked anti-PSMA antibody, see attached Exhibit B. (PSA levels allow rapid clinical evaluation of potential clinical efficacy, see Nanus et al., first paragraph, right hand column, page S87.)

While the claims are directed to non-prostate cancer, the prostate cancer data is relevant. If the barriers proposed by Jain et al. did in reality significantly affect the action of an anti-PSMA antibody one would not expect anti-PSMA antibodies to be effective against prostate cancer. But, as is shown by the Exhibits A and B, the barriers proposed by Jain et al. simply do not act in the way argued by the Examiner.

The Examiner also rejects claims 68 to 73 and 82-111 since "applicants do not state that all restrictions upon public access to the deposits will be irrevocably removed upon grant of a patent on this application and that the deposits will be replaced if the depository cannot dispense the viable samples."

Without conceding the issue, a Declaration of Availability is filed herewith and asserts that J591, J415, J533 and E99 have been deposited with the ATCC as HB-12126, HB-12109, HB-12101, and HB-12127 and that all restrictions upon public access to the deposits will be irrevocably removed upon grant of a patent on this application and that the deposits will be replaced if the depository cannot dispense the viable samples.

The Examiner also rejects claims 66, 73, 75, 79, 81 and 83 under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

Claims 66 and 73 have been amended and claims 75, 79, 81 and 83 have been canceled, thereby obviating this rejection.

For the reasons discussed above, Applicants respectfully request that the Examiner withdraw this rejection.

Obviousness Type Double Patenting

Claims 58-63, 67-69, 84-87 and 107 are rejected "under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,136,311." According to the Examiner,

> although the conflicting claims are not identical, they are not patentably distinct from each other because the currently claimed method of treating non-prostate cancer in a subject comprising providing an antibody or antigen binding portion thereof which binds the extracellular domain of PSMA wherein the antibody or antigen binding portion thereof binds to vascular endothelial cells proximate or within the non-prostate cancerous cells reads on patented claims drawn to methods of killing or ablating non-prostate cancerous cells with a monoclonal antibody to PSMA.

A terminal disclaimer is being filed herewith, thereby obviating this rejection.

Claims 144-171 and 178-181 are provisionally rejected "under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 38, 41, 55-56, 58, 60-63, 65-66, 69, 81-118, 124-174 of copending Application No. 09/357707."

Applicants respectfully traverse this rejection. The claims of the present application are directed to methods of treating cancers using antibodies or antigen binding portions thereof that bind PSMA. The claims of the '707 application are directed to antibodies or antigen binding

portions thereof that bind PSMA. As noted in a restriction requirement issued on April 24, 1998 in U.S. Patent No.6,107,090, from which both the present application and the '707 application claim priority, methods of killing or ablating cancerous cells with an agent that binds PSMA, and the agent itself are patentably distinct from one another. In view of such statements in the parent application, the subsequent applications claimed the methods and the agents as distinct invention. Thus, it is inappropriate to now claim that these two inventions are "not patentably distinct." Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 2/26/04

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